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Cardiovascular effects of repeated nicotine administrations: Identification of pharmacologic conditions where self-sensitization or self-blockade takes place

Silvia L Cruz, Luis A Salazar and Julián E Villarreal. Sección de Terapéutica Experimental, Departamento de Farmacología y Toxicología, CINVESTAV, IPN. Apartado Postal 22026, 14000 México, D F

Tobacco smoking is one of the outstanding risk factors for the production of myocardial infarction and cardiovascular diseases. The tobacco alkaloid nicotine has undesirable effects which predispose to ischemic heart conditions: stimulation of sympathetic ganglia and adrenal glands with increases in heart rate and in blood pressure. There are clinical studies reporting that repeated cigarette smoking produces sustained increases in heart rate (Benowitz et al., 1984). However, classical pharmacology describes the autonomic actions of nicotine as an initial stimulation of autonomic ganglia followed by a more sustained depression. There is, in fact, a general notion in the classical pharmacological literature that the stimulant actions of nicotine show self-blockade (see, for instance, Goldstein et al., 1974).

Our group has previously reported (as have others: Kachur et al., 1986) that in unanesthetized spinal rats the cardiovascular stimulatory actions of nicotine show no self-blockade when nicotine is given in repeated administrations. The purpose of the experiments presented now is to resolve the apparent discrepancy between the concepts of classical pharmacological literature about nicotine self-blockade with the results of clinical studies on repeated cigarette smoking and with our own results of sustained sympathetic stimulation with repeated nicotine administrations.

The effects of repeated injections of nicotine were studied under the following three types of experimental conditions: a) unanesthetized spinal rats; b) spinal rats anesthetized with pentobarbital (60 mg/kg i.p.), and c) intact rats anesthetized with the same dose of pentobarbital.

Nicotine was found to produce dose-related sympathetic effects (25 to 400 µg/kg) in the unanesthetized spinal rat. Pentobarbital markedly reduces sensitivity to the sympathetic stimulant effects of nicotine in the form of a large shift to the right in nicotine's dose-response curves. Self-blockade by nicotine was only observed with extremely high doses 2000 µg/kg and higher) which were only possible to administer in animals under pentobarbital anesthesia; high doses of nicotine produce intracraneal hemorrhages in spinal unanesthetized animals.

In conclusion, in the unanesthetized state, the cardiovascular system is very sensitive to nicotine's sympathetic stimulant effects. The doses of nicotine which produce such stimulant effects are in a range relevant to nicotine concentrations obtained with heavy cigarette smoking. These doses of nicotine do not produce self-blockade but in fact produce self-sensitization. With regard to cardiovascular stimulation, the classical self-blockade by nicotine can be reached only under special conditions of general anesthesia.

References

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